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DOI:

[10.1111/hdi.12500](https://doi.org/10.1111/hdi.12500)

*Document Version*

Peer reviewed version

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*Citation for published version (APA):*

Chilcot, J., Friedli, K., Guirguis, A., Wellsted, D., Farrington, K., & Davenport, A. (2017). C reactive protein and depressive symptoms in haemodialysis patients: a questionable association. *Hemodialysis International*, 21(4), 542-548. DOI: 10.1111/hdi.12500

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## **C reactive protein and depressive symptoms in haemodialysis patients: a questionable association**

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short title CRP and depression in dialysis patients

key words C reactive protein; depression; BDI-II; PHQ-9; dialysis; inflammation

Funding: National Institute for Health Research programme, Research for Patient Benefit. (PB-PG-0110-21073). Ethics approval 12/LO/1554 Trial registration ISRCTN06146268

Conflicts of interest : no author has any conflicts of interest to declare

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## Abstract

## Introduction

Patients with advanced chronic kidney disease (CKD) on haemodialysis (HD) may have increased C reactive protein (CRP) values and depressive symptoms. There is debate about the strength and nature of previously reported associations. We investigated these issues in a cohort of patients on HD.

## Methods

We screened for depressive symptoms using two validated depression screening tools: the Beck Depression Inventory-II (BDI-II), Patient Health Questionnaire (PHQ-9). Demographic and clinical correlates of depression symptoms were evaluated in adjusted linear and logistic regression models, which included extra renal comorbidity and high CRP ( $>5$  mg/L).

## Findings

396 HD patients were studied; 63.1% male, mean age  $63.1 \pm 16.4$  years, median CRP 6 (5-15) mg/l. Depression scores were similar in those with normal and high CRP (BDI-II (9(5-17) vs 11(6-20)) or PHQ (4(2-9) vs 6(2-10)). In adjusted multivariable regression BDI-II scores were associated with previous history of depression ( $\beta$  10.8,  $p < 0.001$ ), serum albumin ( $\beta$  0.41,  $p < 0.001$ ), anuria ( $\beta$  2.4,  $p < 0.037$ ), diabetes ( $\beta$  2.7,  $p = 0.033$ ) and age ( $\beta$  -0.10,  $p = 0.009$ ). High CRP was not independently associated with BDI-II ( $\beta$  2.20,  $p = 0.057$ ), though was with PHQ-9 ( $\beta$  1.20,  $p = 0.046$ ). In logistic regression those with

high CRP were 1.9 times more likely to score  $\geq 16$  on BDI-II screening ( $p=0.016$ ), but did not relate significantly to a PHQ-score  $\geq 10$ .

## Discussion

A relationship was observed between CRP and depression symptoms, though the effect was small, of unlikely clinical significance, and inconsistent between depression measures. Previous reports of this association may reflect overlap between symptoms of depression and advanced CKD.

## Introduction

Major depressive and mood affective disorders are more common in patients with chronic diseases. As many chronic diseases, such as cancer, rheumatoid arthritis, chronic pulmonary disease and heart failure are associated with elevated markers of systemic inflammation, an association between depressive illnesses and mood affective disorders and markers of systemic inflammation have been recognised for some years [1]. The capillaries at the base of the median eminence are fenestrated, allowing direct passage of circulating cytokines and other inflammatory mediators into the brain, and meta-analysis of studies has suggested that raised circulating inflammatory markers, including C-reactive protein (CRP) have an association with the subsequent development of depressive symptoms [2], and also influence the development and progression of major depressive disorders [3], and reduce the response to treatment [4].

Patients with CKD treated by dialysis have increased morbidity and mortality, and as dialysis does not replace normal kidney function, patients are required to comply with dietary and fluid restrictions, and a high pill burden. Although reports suggest that depression, is common amongst dialysis patients, with prevalence varying between 39% based on self-reported screening and 23% based on psychiatric interview [5], and depressed haemodialysis patients are at greater risk of mortality [6]. However depression is more difficult to diagnose because of the overlap of symptoms between depression and those associated with end stage kidney disease [7].

Although systemic inflammation, most commonly assessed by measuring CRP, is often present in haemodialysis patients, studies investigating a link between increased CRP and depressive symptoms in this population have been mixed, with some studies reporting a positive association [8,9], whereas others found no association [10,11]. To investigate whether there was an association between CRP and depressive symptoms we reviewed CRP results in a cohort of haemodialysis patients screened for depressive symptoms as part of the ASSERTID study [12], using the Beck Depression Inventory (BDII) [13] and Patient Health Questionnaire - 9 (PHQ-9) [14].

## Methods

396 patients from the Royal Free Hospital, north London and the Lister Hospital in Hertfordshire, UK were recruited into a screening trial for depression. Patients established on haemodialysis for more 3 months were eligible to enter the study. There were no other exclusion criteria apart from the ability to read and understand English. Consenting patients completed Beck Depression Inventory (BDI-II) and Patient Health Questionnaire-9 (PHQ-9) [13,14] during their haemodialysis session. Previous work with this screening questionnaires for depression has recommended a cut off score of 16 or greater for the BDI-II and 10 or greater for the PHQ-9 for the diagnosis of self-reported depression [13,14]. Patient demographics and co-morbidity were recorded from computerised medical records.

Blood tests were taken routinely pre-dialysis on a monthly basis and results of haemoglobin, serum albumin, calcium, phosphate, CRP and calculation of dialysis adequacy by assessment of urea clearance (Kt/Vurea) closest to the day that questionnaires were completed were analysed. As two different methods were used to measure CRP (Royal Free Hospital (CRPL3, C-Reactive Protein Gen.3, Roche Cobas c 702, Roche Diagnostics, Berkhamstead, UK; Lister Hospital (immunoturbidimetric method, Olympus 2700 AU multi-analyser, Melville, New York, USA)), we divided patients into those with a CRP within the normal reference range for both assays (1-5 mg/L) and those with an increased CRP (> 5 mg/L).

## Ethics

All patients provided appropriate informed consent in keeping with the Helsinki agreement, prior to receiving questionnaires. The study received ethical approval (National Research Ethics Service Committee London - Bentham, reference 12/LO/1554), and was registered (ISRCTN06146268).

## Statistical analysis

Data is reported as mean and standard deviation, or median and interquartile range, or percentage and intergroup analysis was by student's t test, or Mann Whitney U test, or Chi square test with correction for repeated tests (Bonferroni or Dunn's test) and for small numbers, where appropriate. Univariate association was with Spearman correlation. Multivariate linear regression for determinants of BDI-II and PHQ-9 were evaluated. Models were adjusted for variables which had a univariate relationship with the dependent variables, or thought to be clinically relevant determined a priori. These covariates were variables considered included; age, sex, increased CRP ( $>5\text{mg/L}$ ), diabetic status, medical history of heart disease, amputation, stroke, cancer, ethnicity, months since starting HD, urine output, previous history of depression and serum albumin. Similarly logistic regression analysis was used to define determinants of high BDI-II ( $\geq 16$ ) and PHQ-9 ( $\geq 10$ ) scores. These cut-offs were used based upon based validation studies of diagnosing depression in dialysis patients [15,16,17]. Analyses were performed with Graph Pad Prism (Graph Pad Prism V6.0, San Diego, USA) and SPSS 22 (SPSS 22, University Chicago, Illinois, USA). Statistical significance was taken as  $p < 0.05$ . Tables presenting the regression analysis only show significantly variables in addition to CRP; although these were models were fully adjusted for the covariates described above.

## Results

396 patients were screened for depression and had CRP measured. 390 completed the PHQ9 questionnaire, 389 the BDI-II. The mean age was  $63.1 \pm 16.4$  years. 63.1% male. 197 were married or lived with a civil partner, 85 were single, 44 divorced, 11 separated, and 55 widowed. The main ethnic groups were Caucasoid 235, South Asian 57, African-Afro-Caribbean 43 and East Asian 44. In terms of co-morbidity 34.9% of patients were diabetic, 31.1% a history of heart disease, 11.4% malignancy, 8.5% chronic lung disease, 5.8% previous cerebrovascular disease and 3.5% amputation. Eighty eight patients (22.3%) had a past history of depression, 68 (17.2%) had been previously treated with antidepressants and 18 (4.5%) psychological therapy. Weight was  $75.5 \pm 18.8$  kg, with a mean arterial blood pressure pre dialysis of  $99.4 \pm 16.5$

and post-dialysis  $92.3 \pm 16.4$  mmHg. Mean haemoglobin was  $111.1 \pm 12.1$  g/l, serum albumin  $38.3 \pm 4.3$  g/l, corrected calcium  $2.28 \pm 0.20$  mmol/l, phosphate  $1.60 \pm 0.49$  mmol/l, and median CRP 6 (5-15) mg/L. The median BDI-II score was 10 (5-19), and PHQ-9 5 (2-10), with 121 (31.1%) patients having a BDI score of  $\geq 16$ , and 108 (27.8%) with a PHQ score of  $\geq 10$ .

We divided patients into a normal CRP group ( $\text{CRP} \leq 5$  mg/L) and a high CRP group ( $> 5$  mg/L). Groups were relatively well matched in terms of demographics (table 1), although the high CRP were older and had a greater number of Caucasoids, but CRP values were not statistically significantly different between the individual ethnic groups. The high CRP group had lower haemoglobin concentration and serum albumin (table 1). Although more patients with high CRPs were living alone, there were similar numbers of those divorced (normal CRP 18 vs high CRP 36), married or civil partnership (103 vs 94), single (46 vs 39), widowed (18 vs 37),  $\chi^2=11.7$ ,  $p=0.057$ . Education levels; no qualifications, school and university or other qualifications were similar between the groups ( $\chi^2=3.5$ ,  $p=0.83$ ).

There were no differences between the normal and high CRP groups in terms of previous history of depression, or treatments, and no significant differences between BDI-II, or PHQ9 scores (table 1).

### *Adjusted regression models*

To investigate further whether there was an association between CRP and depression we first performed simple correlation analyses, and found no statistical association between serum CRP and either BDI-II and PHQ9 scores. We then constructed multivariable models incorporating those factors associated with BDI-II and PHQ9 scores (Tables 1 and 2). As there was no association with CRP (log transformed) as a continuous variable, we then chose to use a CRP cut off of  $> 5$  mg/L. We found a positive association between the BDI-II score and previous history of depression, serum albumin, anuria and diabetes, and a negative association with age. An increased CRP ( $> 5$  mg/L) was retained in the model, but failed to achieve statistical significance ( $p=0.057$ ) (table 3). Similarly for PHQ9 there was an association with past



history of depression, serum albumin, anuria, diabetes, white ethnicity and increased CRP (table 4). We then performed binomial logistic, which demonstrated association between an increased BDI II score  $\geq 16$  and previous depression, age, serum albumin, anuria and also increased CRP ( $> 5\text{mg/L}$ ) (table 5). . Those with a CRP $>5\text{ mg/l}$  were 1.9 times more likely to score  $\geq 16$  on the BDI-II ( $p=0.016$ ).

A similar model for increased PHQ9 ( $\geq 10$ ), showed an association with past depression, serum albumin, but increased CRP was not statistically significant (table 6).

## Discussion

CRP production by the liver is increased in inflammatory states, and as such we expected to find an association between increasing CRP with a lower serum albumin and haemoglobin concentration. Many chronic diseases, including chronic heart failure, lung disease and rheumatoid arthritis, which impair physical function and activity are associated with increased prevalence of depressive symptoms are also associated with chronic inflammation and an increased serum CRP [2,3]. As such there is an association between increased CRP and depressive symptoms, but this does not necessarily infer causality [4].

In keeping with earlier reports using screening questionnaires to determine the prevalence of depression in haemodialysis patient populations we found that 121 (31.1%) of patients had a BDI score of  $\geq 16$ , and 108 (27.8%) a PHQ score of  $\geq 10$  [5,7,8]. These self-reported questionnaires have been previous validated and use a cut-off point of  $\geq 16$  and  $\geq 10$  for the diagnosis of depressive symptoms [13,14]. Whereas previous studies using these and other screening questionnaires have variously reported a positive association between depression and increased CRP [8,9], or found no association [10,11]. Our study was larger than previous reports, and involved two centres; one serving an inner city London centre and the other outside London, and we found no simple univariate association between serum CRP and depression using BDI-II, and PHQ-9 screening questionnaires.

Looking at individual components of the BDI-II score, we found increased reporting of changes in sleep pattern and appetite which overlap with symptoms

associated with CKD. As such our study highlights the difficulty of measuring depression in haemodialysis patients using screening questionnaires developed for the general population, due to the overlap of symptoms between depression and those associated with end stage kidney disease [7,16]. Many kidney dialysis patients complain of physical tiredness, mental fatigue and have reduced physical activity [18], which often do not improve following the initiation of dialysis therapy, and may even be made worse by haemodialysis treatments [19,20]. Patients with chronic kidney disease treated by haemodialysis are more likely to suffer protein energy wasting leading to muscle loss [21], and reduced muscle mass is associated with reduced physical activity and energy expenditure [22], so increasing weakness and fatigue.

The BDI-II score was associated with younger age, higher serum albumin and anuria. The association between loss of residual renal function and depression has been reported previously [23]. Loss of residual renal function impacts on quality of life for the dialysis patient by increasing dietary and fluid restriction, coupled with potentially greater need for more dialysis therapy, in terms of longer duration of haemodialysis treatment sessions and more frequent attendance for dialysis. Hence the relationship between residual renal function and depression is not altogether surprising. Patients with both higher BDI-II and PHQ9 scores had been treated by haemodialysis for longer. Although there is an overlap between longer duration of dialysis and increased risk of loss of residual renal function, patients with longer dialysis vintage may have additional worries about failure to be transplanted and greater exposure to the complications of haemodialysis, in terms of vascular access failures and infections [24].

Our results are in keeping with previous smaller single centre reports, suggesting that younger healthier dialysis patients are more likely to self-report depressive symptoms, whereas older more co-morbid patients report fewer symptoms [23,25]. We also found an association with diabetes and increasing BDI-II score, this may be because both dialysis and diabetes impose restrictions on dietary intake, and on one hand dialysis impacts on diabetic control, and on the other residual renal function is often more rapidly lost with diabetic kidney disease [26]. Although an increased CRP

was retained in the model, CRP was not a significant independent factor. In a multivariable model using PHQ9 scores, we found similar associations to the BDI-II, although in this case an increased CRP was associated with increasing PHQ9 scores. On logistic regression though a high CRP was associated with a high BDI-II score ( $\geq 16$ ) [13], the association with increased PHQ9 score ( $\geq 10$ ) was not significant. There are some differences between the questionnaires, with 4 of the 9 PHQ-9 questions relating to difficulty with sleeping, lack of energy, poor appetite, moving slowly or having restlessness, which can be commonly reported by dialysis patients unrelated to depression. Whereas the BDI-II having 21 questions, with different scores relating to severity of replies, with 4 questions relating to difficulty with sleeping, lack of energy, fatigue and poor appetite. As such there may be a greater overlap between symptoms associated with chronic kidney disease [27] and the PHQ-9 compared to the BDI-II. Although the brain is protected by the blood-brain barrier, capillaries at the base of the median eminence are fenestrated, so permitting entry of inflammatory mediators into the area of the brain which controls appetite, and potentially alters mood and fatigue [28,29]. Our results support an earlier study showing an association between markers of inflammation and fatigue [27,30,], and this be due to the entry of inflammatory mediators into the brain [28].

Self-reported depression is highly prevalent in chronic HD patients. However there is an overlap between some of the symptoms of chronic kidney failure and questions asked by the screening questionnaires for depression. Similarly chronic kidney disease is a pro-inflammatory condition and CRP concentrations are often increased in HD patients. As such we found that there was an association between an increased CRP and BDI-II score of  $\geq 16$ , although the association was less than that for age, serum albumin, loss of residual renal function and diabetes. Our results are in keeping with those of a recent meta-analysis which shows that depression in advanced CKD is a heterogeneous condition [31]. Since there is a crossover of symptoms between depression and advanced CKD, and it is more likely that sicker patients, with combinations of inflammation, malnutrition and comorbidity who have greater CRP

values and a lower quality of Life, are potentially more likely to self-report depressive symptoms, and as such it may be that previous reports of a direct association between CRP and depression may have been confounded by the tools used for screening for depression, overestimating the effect of CRP.

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**Table 1.** Comparison of clinical and biochemical characteristics between those patients high (> 5mg/L) and normal CRP. Months of haemodialysis treatment (Vintage), dialysis sessional adequacy (Kt/Vurea). Results as numbers, or mean  $\pm$  standard deviation, or median (interquartile range).

Parameter	N	Normal CRP	High CRP	p-value
number		191	205	
Age (years)	396	61 $\pm$ 18	65 $\pm$ 15	0.034
% Male	396	62	64	0.591
% White	396	52	66	0.004
Vintage (months)	357	22 (9-50)	34(12-76)	0.008
% Living Alone	392	28	37	0.043
% Anuric	390	44	52	0.099
% Diabetes	396	35	35	0.926
% Heart Disease	396	26	36	0.043
% Cancer	396	14	9	0.173
Haemoglobin (g/L)	396	113 $\pm$ 12	110 $\pm$ 12	0.008
Albumin (g/L)	396	39.3 $\pm$ 4.1	37.4 $\pm$ 4.3	<0.001
Kt/Vurea	394	1.43 $\pm$ 0.30	1.37 $\pm$ 0.30	0.058
Previous depression	396	39	49	0.251
Previous antidepressants	396	27	41	0.158
Previous psychotherapy	396	12	6	0.174
BDI-II Score	389	9 (5-17)	11 (6-20)	0.076
PHQ-9 Score	390	4 (2-9)	6 (2-10)	0.082

**Table 2.** Comparison of clinical and biochemical parameters in those patients with high ( $\geq 16$ ) BDI-II and PHQ ( $\geq 10$ ) scores and with lower levels. Months of haemodialysis treatment (Vintage), dialysis sessional adequacy (Kt/Vurea). Results as mean  $\pm$ SD, or median (interquartile range) or percentage (%). \*  $p < 0.05$ , \*\*  $< 0.01$ , \*\*\*  $< 0.001$  BDI  $< 16$  vs  $\geq 16$  and PHQ  $< 10$  vs  $\geq 10$ .

Parameter	N	BDI $< 16$	BDI $\geq 16$	PHQ9 $< 10$	PHQ9 $\geq 10$
Age (years)	385	65 $\pm$ 16***	58 $\pm$ 16	65 $\pm$ 16***	60 $\pm$ 16
% Male	385	61	69	62	66
% White	384	62	44	52*	42
Vintage (months)	357	24 (9-56)*	40 (17-76)	25 (10-57)*	39 (14-76)
% Living Alone	383	34	32	33	34
% previous depression	385	13***	57	15***	42
% Anuric	381	44*	57	45*	57
% Diabetes	385	33	35	33	39
% Heart Disease	385	31	31	31	32
Haemoglobin (g/L)	385	111 $\pm$ 12	111 $\pm$ 12	111 $\pm$ 12	110 $\pm$ 12
Albumin (g/L)	385	38.5 $\pm$ 4.2**	39.3 $\pm$ 4.3	38.1 $\pm$ 4.3	38.8 $\pm$ 4.5
Kt/V	385	1.40 $\pm$ 0.28	1.38 $\pm$ 0.35	1.41 $\pm$ 0.3	1.37 $\pm$ 0.3
% CRP $> 5$ mg/l	385	50	58	50	58



Table 3. Multivariable regression model for BDI-II scores adjusted for covariates (Tables 1 and 2; age, white ethnicity, heart disease, diabetes haemoglobin, albumin, anuria, past history of depression, living alone, dialysis vintage, CRP >5 mg/L). Model fit  $r=0.54$ ,  $r^2=0.25$ , adjusted  $r^2=0.23$ , Durbin Watson 1.82. Standard error of  $\beta$  (StE  $\beta$ ), exponential  $\beta$  (exp  $\beta$ ), 95% confidence limits (5% CL and 95%CL). Past medical history (PMH), C reactive protein (CRP).

variable	$\beta$	StE $\beta$	Exp $\beta$	t	5% CL	95% CL	p
PMH depression	10.8	1.32	0.40	8.2	8.2	13.4	<0.001
Age years	-0.10	0.04	-0.14	-2.6	-0.17	-0.25	0.009
Albumin g/L	0.41	0.14	0.17	3.1	0.16	0.73	0.002
Diabetes	2.7	1.24	0.11	2.2	0.22	5.1	0.033
Anuria	2.4	1.15	0.11	2.1	1.46	4.72	0.037
CRP > 5 mg/L	2.2	1.14	0.10	1.9	0.67	4.41	0.057

Table 4. Multivariable regression model for PHQ9 score adjusted for covariates (Tables 1 and 2). Model fit  $r=0.47$ ,  $r^2=0.252$  adjusted  $r^2=0.20$ , Durbin Watson 1.97. Standard error of  $\beta$  (StE  $\beta$ ), exponential  $\beta$  (exp  $\beta$ ), 95% confidence limits (5% CL and 95%CL). Past medical history (PMH), C reactive protein (CRP).

variable	$\beta$	StE $\beta$	Exp $\beta$	t	5% CL	95% CL	p
PMH depression	5.3	0.69	0.38	7.6	3.93	6.68	<0.001
Albumin g/L	0.2	0.08	0.15	2.7	0.06	0.36	0.006
Anuria	1.3	0.62	0.11	2.1	0.10	2.52	0.034
Diabetes	1.3	0.66	0.11	2.9	0.05	2.63	0.042
White ethnicity	1.3	0.64	0.11	2.0	0.04	2.56	0.043
CRP > 5 mg/L	1.2	0.60	0.10	2.0	0.02	2.39	0.046

Table 5. Logistic regression model for BDI-II score  $\geq 16$  adjusted for covariates (Tables 1 and 2). Model fit Nagelkerke  $r^2 = 0.26$ . Standard error of  $\beta$  (StE  $\beta$ ), exponential  $\beta$  (exp  $\beta$ ), 95% confidence limits exp  $\beta$  (5% CL and 95%CL). Past medical history (PMH), C reactive protein (CRP).

variable	$\beta$	StE $\beta$	Wald	Exp $\beta$	5% CL	95% CL	p
PMH depression	1.6	0.30	3.2	5.1	2.84	9.03	<0.001
Albumin g/L	0.1	0.04	12.7	1.1	1.06	1.22	<0.001
Age years	-0.1	0.01	5.7	0.9	0.96	0.99	0.017
CRP > 5 mg/L	0.7	0.28	5.8	1.9	1.13	3.34	0.016

Table 6. Logistic regression model for PHQ9 score  $\geq 10$  adjusted for covariates (Tables 1 and 2). Model fit Nagelkerke  $r^2 = 0.20$ . Standard error of  $\beta$  (StE  $\beta$ ), exponential  $\beta$  (exp  $\beta$ ), 95% confidence limits exp  $\beta$  (5% CL and 95%CL). Past medical history (PMH), C reactive protein (CRP).

variable	$\beta$	StE $\beta$	Wald	Exp $\beta$	5% CL	95% CL	p
PMH depression	1.5	0.29	26.9	4.6	2.58	8.1	<0.001
Albumin g/L	0.7	0.04	4.2	1.1	1.00	1.15	0.04
CRP > 5 mg/L	0.4	0.46	2.4	1.5	0.89	2.63	0.12

